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EXAMINER
COLEMAN, BRENDA LIBBY

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/701,893	Applicant(s) BIGG et al.
	Examiner Brenda Coleman	Art Unit 1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *3-5 and 9-11* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *3-5 and 9-11* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 1

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Claims 3-5 and 9-11 are pending in the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 3, 4, 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of the method claims are not adequately enabled solely based on its inhibitory effect on the somatostatin receptors provided in the specification. Recent studies on experimental and clinical pharmacology of somatostatin receptors cited in Annual Reports in Medicinal Chemistry indicate that the following disorders are **expected** to have utility associated with somatostatin receptors: diabetes and diabetic retinopathy, nephropathy, and neuropathy, pain, migraine, restenosis and chromic rejection, rheumatoid arthritis, etc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In addition to other disorders which are difficult to treat these claims call for the treatment of cancer. However, there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to treat

cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied upon are reasonably predictive of *in vivo* efficacy by those skilled in the art. See *In re Ruskin*, 148 USPQ 221; *Ex parte Jovanovics*, 211 USPQ 907; MPEP 2164.05(a).

Patent Protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure. *Genentech Inc. v. Novo Nordisk* 42 USPQ2d 1001.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 3-5 and 9-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claims 3, 4, 9 and 10 are vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the diseases capable of being mediated by inhibiting the activity of somatostatin receptors. Octreotide has been used experimentally as discussed on page 211 of "Annual Reports". Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties *in vitro*, when administered to a patient with a certain disease, does not produce a favorable response. One can not conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given

drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration can not be predicted in advance. Should our drug be given as a bolus *iv* or in a time release *po* formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active *in vitro*, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of whom are inhibitors *in vitro*, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property which the second drug is capable. It is common for a drug, particularly in diabetes, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to effect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

b) Claims 10 (and claims dependent thereon) are vague and indefinite in that it is not known what is meant by cyclo**alkly** in the definition of the substituents on R.

c) Claims 10 (and claims dependent thereon) are vague and indefinite in that it is not known what is meant by =O and =S in the definition of Z. It is believed that the applicants intended -O- and -S-.

d) Claims 10 (and claims dependent thereon) are vague and indefinite in that it is not known what is meant by the period which appears before the definition of R_{2a} and R_{2b} indicating the end of the claim which is not so.

608.01(m) Form of Claims [R - 3]

The claim or claims must commence on a separate sheet and should appear after the detailed description of the invention. While there is no set statutory form for claims, the present Office practice is to insist that each claim must be the object of a sentence starting with "I (or we) claim", "The invention claimed is" (or the equivalent). If, at the time of allowance, the quoted terminology is not present, it is inserted by the clerk. Each claim begins with a capital letter and ends with a period. **Periods may not be used elsewhere in the claims except for abbreviations**. See Fressola v. Manbeck, 36 USPQ2d 1211 (D.D.C. 1995). ** Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation, 37 CFR 1.75(i).

e) Claims 10 (and claims dependent thereon) are vague and indefinite in that it is not known what is meant by the "or" between the moieties heteroaryl and heteroarylalkyl in the definitions of R_{22} and R_{23}. The "or" indicates in the end of the markush group which is not so.

f) Claims 10 (and claims dependent thereon) recites the limitation "said pathological disorders" in the last line of the claim. There is insufficient antecedent basis for this limitation in the claim.

g) Claim 11 is vague and indefinite in that it is not known what is meant by -(Y)C-X'-R' in the proviso labeled b). It is believed that the applicants intended -C(Y)-X'-R'.

h) Claim 11 is vague and indefinite in that it is not known what is meant by X' is hydrogen in the proviso labeled iiiii), since X' at no time is hydrogen.

i) Claim 9 is vague and indefinite in that it is not known what is meant by the composition claim which states "a compound of claim 10", however, claim 10 is a method claim not a compound claim.

j) Claim 3 is vague and indefinite in that it is not known what is meant by "ter-butyl" in the definition of the substituents for R.

k) Claim 5 is vague and indefinite in that it is not known what is meant by "2-terBu-Ph" in the definition of R on page 47, line 12.

l) Claim 5 is vague and indefinite in that it is not known what is meant by "ter-butyl" in the definition of the substituents for R.

m) Claim 5 is vague and indefinite in that it is not known what is meant by the definition of $R_{2a'}$ and $R_{2b'}$.

n) Claim 5 is vague and indefinite in that it is not known what is meant by the period which appears before the provisos indicating the end of the claim which is not so.

o) Claim 5 is vague and indefinite in that it is not known what is meant by "4-terbutylphenyl" and "2,4-diterbutylphenyl" in the third and fourth proviso.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 5 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Prunonosa et al., Journal of Chromatograph. Prunonosa teaches the compounds of the instant invention where R_1 is Cl; R_{2a} and R_{2b} are hydrogen; R_3 is methyl; and W is (4-hydroxy-phenyl)-NH-CO-. See CAPLUS printout herein provided.

4. Claims 5 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Girault et al., Chromatographia. Girault teaches the compounds of the instant invention where R_1 is Cl; R_{2a} and R_{2b} are hydrogen; R_3 is methyl; and W is (4-hydroxy-phenyl)-NH-CS-. See CAPLUS printout herein provided.

5. Claims 5 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Weber et al., EP 0 503 471. Weber teaches the compounds of the instant invention where R_1 is Cl; R_{2a} is hydrogen or methyl; R_{2b} is hydrogen or methyl; R_3 is methyl; and W is (4-chloro-phenyl)-CO-, (4-i-butyl-phenyl)-CO-, (4-methyl-phenyl)-CO-, (4-n-butyl-phenyl)-CO-, (4-tert-butyl-phenyl)-CO-, (4-methoxy-phenyl)-CO-, (2,3,4,5,6-pentafluoro-phenyl)-CO-, (4-trifluoromethyl-phenyl)-CO-, phenyl-CO-, (4-ethyl-phenyl)-CO-, pyridyl, etc.

6. Claims 5 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Braquet et al., FR 2660311. Braquet teaches the compounds of the instant invention where R_1 is Cl; R_{2a} and R_{2b} are hydrogen; R_3 is methyl; and W is (2,4-difluoro-phenyl)-NH-CO- and (2-chloro-phenyl)-NH-CS-. See pages 199 and 203 on CAPLUS printout herein provided.

7. Claims 5 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Miyazawa et al., Chem. Pharm. Bull. Miyazawa teaches the compounds of the instant invention where R_1 is Cl; R_{2a} and R_{2b} are hydrogen; R_3 is methyl; and W is (2-methoxy-phenyl)-CO- and (4-fluoro-phenyl)-CH_2-CO-. See CAPLUS printout herein provided.

8. Claim 11 is rejected under 35 U.S.C. 102(b) as being anticipated by Okano et al., EP 0 367 110. Okano teaches the compounds of the instant invention where R_1 is Cl; R_{2a} and R_{2b} are hydrogen; R_3 is methyl; and W is (4-fluoro-phenyl)-CH_2-CO- and phenyl-CH_2-CO-.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 3-5 and 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tahara et al., EP 0 638 560. The generic structure of Tahara encompasses the instantly claimed compounds (see Formula I, page 4) and for the same use (see page 3, line 4) as claimed herein. Example 52, 306-319, 371, etc. differ only in the nature of the W, R^{17} and R^{18} substituents. Page 4 defines the substituent W as -N(R^{36})-, -O- or -S- and R^{17} and R^{18} are defined on page 8, lines 17-19 as combinedly form a 5, 6 or 7-membered hetero ring which may have oxygen, sulfur or -N(Rb^{30})-. Compounds of the instant invention are generically embraced by Tahara in view of the interchange ability of the W, R^{17} and R^{18} substituents of the tetracyclic ring system. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to select for ethoxyphenyl as well as other possibilities from the generically disclosed alternatives of the reference and in so doing obtain the instant compounds in view of the equivalency teachings outlined above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Coleman whose telephone number is (703) 305-1880. The examiner

can normally be reached on Mondays and Tuesdays from 9:00 AM to 3:00 PM and from 5:30 PM to 7:30 PM and on Wednesday thru Friday from 9:00 AM to 6:00 PM.

The fax phone number for this Group is (703) 308-4734 for "unofficial" purposes and the actual number for **OFFICIAL** business is **308-4556**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Brenda Coleman

Brenda Coleman
Primary Examiner AU 1624
December 16, 2001